

REMARKS

In this application, claims 21-143 were pending, with claims 21-118 and 133-143 withdrawn as drawn to non-elected subject matter. By this amendment, Applicants cancel claims 21-32, 36, 37, 39-41, 49, 60-118, 133-136, and 143 without prejudice. Applicants also amend claims 119, 120, and 125-131 and submit new claims 144-171, relating to the elected subject matter which involves modified GDF-8 propeptide polypeptides. Additionally, withdrawn claims 33, 38, 137, and 142 are amended herein, as they relate to a process of making or using the claimed products, and may be available for rejoinder upon allowance of the product claims currently under examination (see MPEP § 821.04). After amendment, claims 33-35, 38, 42-48, 50-59, and 137-142 stand withdrawn, and may be available for rejoinder. Claims 119-132 and 144-171 are pending and relate to originally elected subject matter.

The amended claims are submitted in response to a telephonic interview with the Examiner to determine whether the amended claims presented above are allowable. Applicants thank the Examiner for discussing the new claims.

Applicants submit that the amendments do not introduce new matter. New claims 144-171 are drawn to particular embodiments of the invention. The claims are amended to refer to SEQ ID NO:5, the propeptide portion of SEQ ID NO:1. The correspondence of SEQ ID NOs:1 and 5 is described in detail below. Exemplary support for the amendments to the claims is found, for example, at page 7, lines 7-13 (homologs); page 8, lines 19-23 (biological activities of GDF-8 propeptide); page 9, lines 23-24 ("mutation"); page 17, line 1 to page 18, line 2 (modified GDF-8 propeptides,

including biologically active fragments and percent identity to SEQ ID NO:5); page 23, lines 21-28 (biologically active fragments of GDF-8 propeptide); page 24, line 6 to page 25, line 7 (propeptides and fragments having biological activity); and in the claims as filed.

Asp-99 of SEQ ID NO:1 Corresponds to Asp-76 of SEQ ID NO:5

Please note that in amended claim 119, the aspartate residue corresponding to Asp-99 in SEQ ID NO:1 (human GDF-8 precursor sequence) is now identified as the aspartate residue corresponding to position 76 of SEQ ID NO:5 (human GDF-8 propeptide sequence) in order to simplify the sequence references in the amended claim set. Similarly, new claims 144-171 refer to SEQ ID NO:5 to simplify the sequence references. Support for this amendment is found, for example, at page 23, line 26 to page 24, line 2 and at page 50, lines 14-16, as well as in the Sequence Listing at pages 1 and 5. These passages show that amino acids 24-266 of SEQ ID NO: 1 (human GDF-8 propeptide sequence), are amino acids 1-243 of SEQ ID NO:5. The passages also show that position 76 of SEQ ID NO:5 corresponds to position 99 of SEQ ID NO:1. Thus, disclosure of a mutation modifying Asp 99 of SEQ ID NO:1, for example, at page 18, lines 21-24 and in Table 2, discloses a mutation modifying Asp 76 of SEQ ID NO:5.

35 U.S.C. § 112, second paragraph

The previous claims were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Without acquiescing in the prior grounds for rejection, the previously pending claims are herein amended, and the term "at least one mutation at

an aspartate residue” is deleted from claim 119, to clarify that a mutation modifying the aspartate residue corresponding to Asp 76 of SEQ ID NO:5 is claimed, such as by a deletion, substitution, or insertion mutation (see page 9, lines 23-24). Further, the present claims include functional limitations and recite the sequence identifier, SEQ ID NO:5, to clarify the “modified” GDF-8 propeptides that are claimed. “Modified GDF-8 propeptide” is defined and clearly set forth in the specification, for example at page 9, line 18 to page 10, line 2. The present claims expressly recite functional and structural characteristics of the modified propeptides as described in the specification, to more clearly set forth the scope of the claimed subject matter.

Also, while claim 131 is not rejected on this basis, “modified” is added to claim 131 to clarify and correct the antecedent basis, as “GDF-8 propeptide” is used herein and in the specification to encompass modified and unmodified forms of the polypeptide. Accordingly, Applicants submit that the claims are not indefinite.

35 U.S.C. § 112, first paragraph

The Examiner had rejected the prior claims as not adequately described and enabled, objecting that in former claims 119-132: “There is no limitation on the degree of variation allowed by the claims, and no requirement that the propeptides have any particular function.” As discussed above, Applicants have amended the claims to more clearly recite the intended scope of the claimed subject matter.

Applicants believe that the present claims more clearly set forth the scope of the modified GDF-8 propeptides claimed, and that the present claims are adequately described. Modified GDF-8 propeptides as claimed comprise a mutation at the residue

corresponding to Asp-99 of SEQ ID NO:1 (Asp 76 of SEQ ID NO:5) as set forth at page 18, lines 22-23, for example. Modified propeptides comprising an amino acid sequence at least 75% identical to SEQ ID NO:5 are discussed at page 17, and the various homologs of the human GDF-8 propeptide of SEQ ID NO:5 are described at page 7, lines 4-20. The functional limitations now expressly set forth are described at page 8, lines 19-28, page 20, line 25, and in the experiments of Examples 3-6, for example. Many homologs of the human GDF-8 propeptide sequence of SEQ ID NO:5 and their sequence alignment were known in the art, and are described in the specification at page 7, lines 4-16, for example.

Applicants also believe that the present claims are adequately enabled, and that the disclosure allows one skilled in the art to make and use the invention commensurate in scope with the present claims. The specification discloses that a mutation at Asp-99 of SEQ ID NO:1 will allow increased half-life of a modified GDF-8 propeptide, and the previously submitted declaration shows the in vivo and in vitro phenotype of such a mutation. As amended, the claims clarify that modified GDF-8 propeptides that 1) retain one or more biological properties of a GDF-8 propeptide and 2) have an increased in vivo or in vitro half-life relative to a corresponding unmodified GDF-8 propeptide are within the scope of the claims.

Applicants have shown that modified GDF-8 propeptides comprising a mutation at the residue corresponding to Asp-99 of SEQ ID NO:1 (Asp 76 of SEQ ID NO:5) display unexpectedly beneficial properties (see Wolfman Declaration filed with Response of February 20, 2004, at page 2, ¶¶3 and figures 2-4). One skilled in the art

would apply the description of variations in the amino acid sequence of GDF-8 propeptide to the Asp-99 mutation characterized in the Wolfman Declaration, to readily practice the claimed invention without undue experimentation (see, for example, page 17, line 15 to page 18, line 2 and page 24, lines 10-26 (describing GDF-8 modifications); page 19, line 4 and line 19 (describing an Asp-99 mutation phenotype); and the Wolfman Declaration, functionally characterizing the effect of an Asp-99 change).

The specification describes in detail how to make and use the claimed propeptides (see page 22, line 16 to page 25, line 7). Applicants have provided numerous assays for determining whether a molecule has a biological activity of a GDF-8 propeptide or an increased half-life. One skilled in the art could easily determine whether any other mutation in a modified GDF-8 propeptide also possesses such activity. Accordingly, with the functional limitations now in the claims, the teachings of the specification sufficiently enable one skilled in the art to produce modified GDF-8 propeptides with additional mutations, but which retain one or more biological activities of a GDF-8 propeptide and have an increased half-life relative to a corresponding unmodified GDF-8 propeptide.

Applicants submit that as amended, the pending claims are fully supported and enabled by the specification as filed. One skilled in the art, reading the specification, would understand that Applicants possessed the claimed modified GDF-8 propeptides when the application was filed. Further, the disclosure allows one skilled in the art to

practice the claimed invention without undue experimentation. Accordingly, Applicants submit that the amended claims are adequately described and enabled.

Conclusion


In view of the foregoing remarks, Applicants respectfully request reconsideration and reexamination of the application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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